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Intracranial aneurysms in autosomal dominant polycystic kidney disease

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Intracranial aneurysm in autosomal dominant polycystic kidney disease. Rupture of intracranial aneurysm (ICA) is a rare but severe manifestation of autosomal dominant polycystic kidney disease (ADPKD). In order to assess its natural history, to determine the prevalence of familial aggregation and to document linkage to PKD1 locus, we conducted a retrospective study on 77 ADPKD patients from 64 families presenting with ruptured ($N = 71$) or unruptured ($N = 6$) aneurysm. Information was collected on kidney disease, intracranial aneurysm and family history. Linkage to PKD1 locus was examined by five probes to obtain informative flanking markers. Within one year prior to rupture, blood pressure was normal in 29% of the patients. At the time of rupture, mean age was 39.5 years (range 15 to 69), renal function was normal in half of the patients and 11% were on renal replacement therapy. The ruptured aneurysm was usually located on the middle cerebral artery. Additional intact aneurysms (1 to 6) were detected in 31% of the patients. Surgical or endovascular treatment was performed in 54 (76%) patients whereas 17 (24%) had medical management only. Rupture of ICA was fatal in seven (10%) patients. On long-term follow-up 27 (38%) were left with severe disablement. Five patients bled from another aneurysm 2 days to 14 years after initial rupture. Only two of six patients with unruptured aneurysm alone were treated on a prophylactic basis. No clinical marker associated with aneurysm was found. A family history of aneurysm rupture was demonstrated in 10 (18%) kindreds. Linkage to the PKD1 locus was established in two of three tested families. These data suggest that ICA rupture in ADPKD patients entails significant mortality and morbidity, close to the rates reported in non-ADPKD patients. Prophylactic screening for unruptured aneurysms should focus on patients with a previous episode of rupture, and probably on those with a familial history of aneurysm.

The defective gene responsible for most autosomal dominant polycystic kidney disease (ADPKD) was localized in 1985 to a locus designated PKD1 on the short arm of chromosome 16 [1]. Subsequently, genetic heterogeneity was proven as no linkage with PKD1 was detected in some rare families [2, 3]. Intracranial aneurysm (ICA) is the major vascular abnormality reported in ADPKD. It is widely believed that this association is more frequent than due to chance alone, although its true prevalence has not been adequately assessed. Since the recognition that such aneurysms may progress to rupture [4] leading to subarachnoid, intraventricular or intracerebral hemorrhage, it is considered to be one of the most serious complications of ADPKD [5]. As cerebral hemorrhage frequently occurs without associated aneurysm in patients with ADPKD [6], computed tomography (CT) and/or cerebral angiography are warranted to ascertain the cause of the bleed. Despite substantial improvements in neurological imaging, there is little information on the natural history of ICA in ADPKD patients. Whether the existence of ICA is associated with a particular clinical profile of ADPKD is also unknown. However, the existence of familial clustering of intracranial aneurysms among ADPKD patients has been demonstrated in a recent study [7], although detailed neurological assessment and genetic data were missing.

Within a Concerted Action Group ("Toward the Prevention of Renal Failure caused by Polycystic Kidney Disease"), supported by the European Community, we therefore initiated a multicenter study on ICA in ADPKD with the aims of delineating the profile and outcome of ADPKD patients with ruptured or unruptured ICA, and of performing genetic linkage studies to the PKD1 locus in selected families having several members affected by ICA.

Methods

Patients

We contacted nephrologists in six European countries to identify patients with ADPKD and intracranial aneurysms on a retrospective basis. Diagnosis of ADPKD was supported by both usual clinical and ultrasonographic criteria [8], or on autopsy report. Intracranial aneurysms were identified by cerebral arteriography, cranial computed tomography or both in patients with unruptured or ruptured aneurysms. In patients with intracranial hemorrhage (subarachnoid hemorrhage and cerebral hematoma), bleeding had to be clearly attributed to ruptured aneurysm. Patients with angiogram-negative subarachnoid hemorrhage were excluded from the study.

A detailed questionnaire was then sent to each participating nephrologist. The first patient identified in each family was designated as the index case. The questionnaire sought information on kidney disease including presentation, blood pressure in the year prior to rupture, antihypertensive therapy and renal function. We requested data on the presentation, size and

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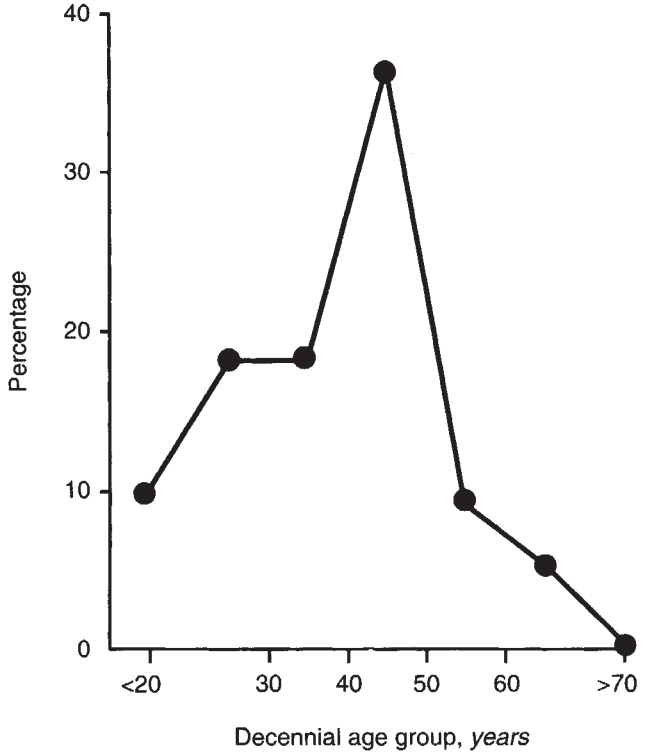

Fig. 1. *Age (in years) distribution of first aneurysmal rupture in 71 ADPKD patients.*

location of ICA on the circle of Willis and its branches, subsequent treatment, recurrent rupture and clinical outcome. Hypertension was defined as blood pressure above or equal to 160 mm Hg systolic or 95 mm Hg diastolic or use of antihypertensive drug. Renal impairment was defined as serum creatinine concentration above 120 μmol/liter. The diagnosis of cerebral aneurysm in relatives with established polycystic kidney disease was considered as proven if identified by arteriography, or probable if intracranial hemorrhage had occurred before 40 years of age.

Linkage analysis

Linkage to the PKD1 locus was examined in three families having two or three relatives with proven intracranial aneurysm. Blood samples from 6, 24 and 14 members were analyzed in families A, B and C, respectively. Standard methods were used for DNA extraction, digestion with restriction enzymes, electrophoresis, Southern blotting and hybridization. A set of five probes (3′ HVR, pGG1, p26.6, VK5b and 218 EP6) provided by the Concerted Action Group was tested to obtain informative flanking markers [9].

The MLINK subprogram of the computer program LINKAGE (version 5.03) was used to calculate lod scores [10]. Two-point analysis lod scores were calculated with the 3′HVR informative marker. Multipoint analysis was performed with the distal marker 3'HVR and one proximal marker (VK5b or 218 EP6).

Table 1. Sites of the ruptured cerebral aneurysms in 71 ADPKD patients presenting with a first rupture

Aneurysm site	Number of cases
Internal carotid artery	4
Anterior communicating artery	12
Middle cerebral artery	30
Anterior cerebral artery	8
Basilar bifurcation of posterior cerebral artery	5
Posterior communicating artery	1
Not specified	11

Results

Data were collected on 77 patients (45 female and 32 male) from 64 families. At the time of diagnosis, aneurysmal rupture had occurred in 71 patients. In the six remaining patients the aneurysm was unruptured.

Ruptured aneurysms

Age at rupture ranged from 15 to 69 years (mean 39.5) and was under 21 years in seven patients (Fig. 1). On admission 51 patients had symptoms of uncomplicated subarachnoid hemorrhage with signs of meningeal irritation only, whereas 20 patients had focal neurological deficits or loss of consciousness.

The diagnostic procedure was cerebral arteriography in 64 patients and cranial CT in 7. The site of aneurysm was specified in 60 cases. All aneurysms were saccular. The ruptured aneurysm was most frequently located on the middle cerebral artery (Table 1). Four-vessel arteriography was performed in 55 patients and disclosed additional intact aneurysms in 17 patients (8 females, 9 males). The size of the ruptured aneurysm was known in nine patients and ranged from 2.5 to 27 mm.

Blood pressure had been recorded in 38 patients within the year prior to aneurysmal rupture. Eleven patients who were not taking antihypertensive therapy had blood pressure below 160/95 mm Hg. At the time of rupture, renal function was known in 64 patients: 32 had normal serum creatinine, 24 had chronic renal failure, six patients were on regular hemodialysis, and two had a functioning kidney graft. Aneurysm rupture led to the diagnosis of previously unknown ADKPD in seven patients.

Following aneurysm rupture, 17 patients did not undergo surgery either because their clinical condition was considered too poor (N = 14, including four patients who died from cerebral hemorrhage within 5 days), or the aneurysm was unclippable because of its location (N = 3). Rebleeding from the same aneurysm occurred subsequently in four patients after an interval of 4 months to 29 years, leading to death in one of them and to successful surgical treatment in another one. At the end of follow-up, among the 17 non-operated patients ten patients had died (5 from aneurysmal rupture and 5 from unrelated conditions) and seven were alive, after a mean follow-up of 8.1 years (range 1 to 30). All but one were without major neurological deficit. Four were on regular dialysis, one had a functioning kidney graft and two had chronic renal failure.

Fifty-four patients received surgical or endovascular treatment. The aneurysm was not clipped in two cases (wrapping in one; endovascular occlusion of the parent vessel in the other). Aneurysmal rupture recurred in both patients, 4 and 15 months later, leading to death in one case and severe deficit in the other.

Table 2. Outcome of 71 ADPKD patients after the first rupture of an intracranial aneurysm

	Early death ≤ 3 months	Survival > 3 months			
		Lost to follow-up	Major sequellae	Good recovery	Late death due to recurrent hemorrhage
Operated (N = 54)	3	2	22	24	3
Non-operated (N = 17)	4	0	5	7	1
Total (N = 71)	7	2	27	31	4

The ruptured aneurysm was clipped in 52 cases; three patients died within three months of the surgical procedure including one who ruptured a second aneurysm located at a mirror site of the Willis circle. Two further patients were lost to follow-up. The 47 remaining patients were followed for a mean of 8.3 years (range 1 to 18 years). Further rupture of another aneurysm occurred in four cases, 6 to 14 years later. In three cases previously reported [11], the second aneurysm was retrospectively not detectable on the four-vessel angiography performed at the time of the initial rupture. One of these patients had two episodes of rebleeding, the third attack leading to death. Two patients were left with severe neurological impairment. The last patient had seven aneurysms on initial angiography, only two of which were clipped. He died from recurrent rupture six years after the first episode. At the end of the follow-up the 43 remaining patients whose aneurysm had been clipped did not have recurrence of ICA rupture. Nineteen patients had persistent severe neurological impairment while 24 were asymptomatic (Table 2).

Renal manifestations related to ADPKD on follow-up included hypertension diagnosed in 79% of the patients at a mean age of 36.4 (range 6 to 60) years, and end-stage renal failure in 29 patients at a mean age of 46 (range 10 to 66) years. Liver cysts and mitral valve abnormalities were observed in 60% (31 of 51) and 22% (9 of 41) of the patients, respectively. No abdominal aortic aneurysm was diagnosed in the 16 patients studied by echography or computed tomography.

To determine whether renal- and extrarenal disease might share an unusual profile in the seven patients whose rupture occurred at a very young age (≤ 20 years), we compared them to the 64 remaining patients. A striking female preponderance (6 of 7) characterized the younger group. There was no statistical difference with respect to the mean number of aneurysms per patient or the family history of aneurysm rupture.

Unruptured aneurysm

Six female patients (mean age 48.5 years, range 24 to 66) with non-ruptured aneurysm were taken as index cases. Manifestations were mass lesions (N = 2), cerebral ischemia (N = 1) or persistent headache with family history of rupture (N = 2), and in one asymptomatic patient the aneurysm was detected by screening. Three of the six had multiple aneurysms, two in two patients and three in one. One patient died after prophylactic surgery. Selective endovascular obliteration was successfully performed in another. One patient was not a suitable candidate for surgery and died of progressive dementia two years after detection of aneurysm. In two patients, aneurysms were unclippable. In the last one, the size of the detected aneurysm was judged too small to carry out surgical repair. Four patients were alive without neurological impairment after a mean follow-up of 1.5 years (range 1 to 2).

In addition, 29 unruptured aneurysms were detected in association with a ruptured aneurysm in 17 patients (see above): 1 in 10, 2 in 5, 3 in 1 and 7 in 1 patients. Nine of these were operated on, without additional morbidity or mortality. Among 20 incidental aneurysms which were initially not operated on, only three bled during a 88 patient-years of follow-up (mean follow-up 4.4 years, range 1 to 17).

Family history

Among 55 pedigrees available, all but one demonstrated a family history of ADPKD. Ten (18%) index patients had a family history of intracranial aneurysm either proven by arteriography (N = 6) or regarded as highly probable (N = 4). Affected relatives were siblings in three families, parents in five and both in two. No father to son transmission was recorded. The mean number of ADPKD affected patients per family was similar in families with (N = 5.2) and without (N = 4.1) family history of aneurysm. Patients of both groups were comparable as regards diastolic blood pressure prior to the rupture, age and serum creatinine at rupture, and number of unruptured aneurysms. Only systolic blood pressure was significantly higher in the group without family history both prior to rupture and at last follow-up (160.1 vs. 131.7 and 144.2 vs. 134.9 respectively, $P < 0.05$).

Interestingly, one index case who presented with subarachnoid hemorrhage at age 20 had a monozygotic twin currently free of stroke at age 48 (Fig. 2, family C). At age 47, both were examined by magnetic resonance (MR) imaging. Two aneurysms were detected in the former (the largest one was clipped) and none in the latter. Hypertension had been untreated in the former and treated for 20 years in the latter.

Genetic linkage study

Lod scores obtained in the two-point linkage analysis in families A, B and C were 0.90, 2.83 and 1.94, respectively (Fig. 2). After multipoint analysis with flanking markers, lod scores increased to 1.01, 3.06 and 2.18, respectively, suggesting linkage to PKD1 locus in at least families B and C.

Discussion

Our primary aim was to shed light on the epidemiology and outcome of intracranial aneurysms in ADPKD patients. Recent studies dealt with asymptomatic ICA [7] or did not consider the long-term follow-up [13]. It may be argued that our retrospective study involves several biases. As demonstration of both polycystic kidney disease and aneurysm rupture were prerequisite for inclusion, we probably missed patients with the mildest forms of renal disease. The most severe forms of intracranial hemorrhage leading to early death before any investigation were not included, and may account for 12 to 20% of aneurysmal rupture in non-ADPKD patients [14]. On the other hand, the mildest forms of uncomplicated subarachnoid

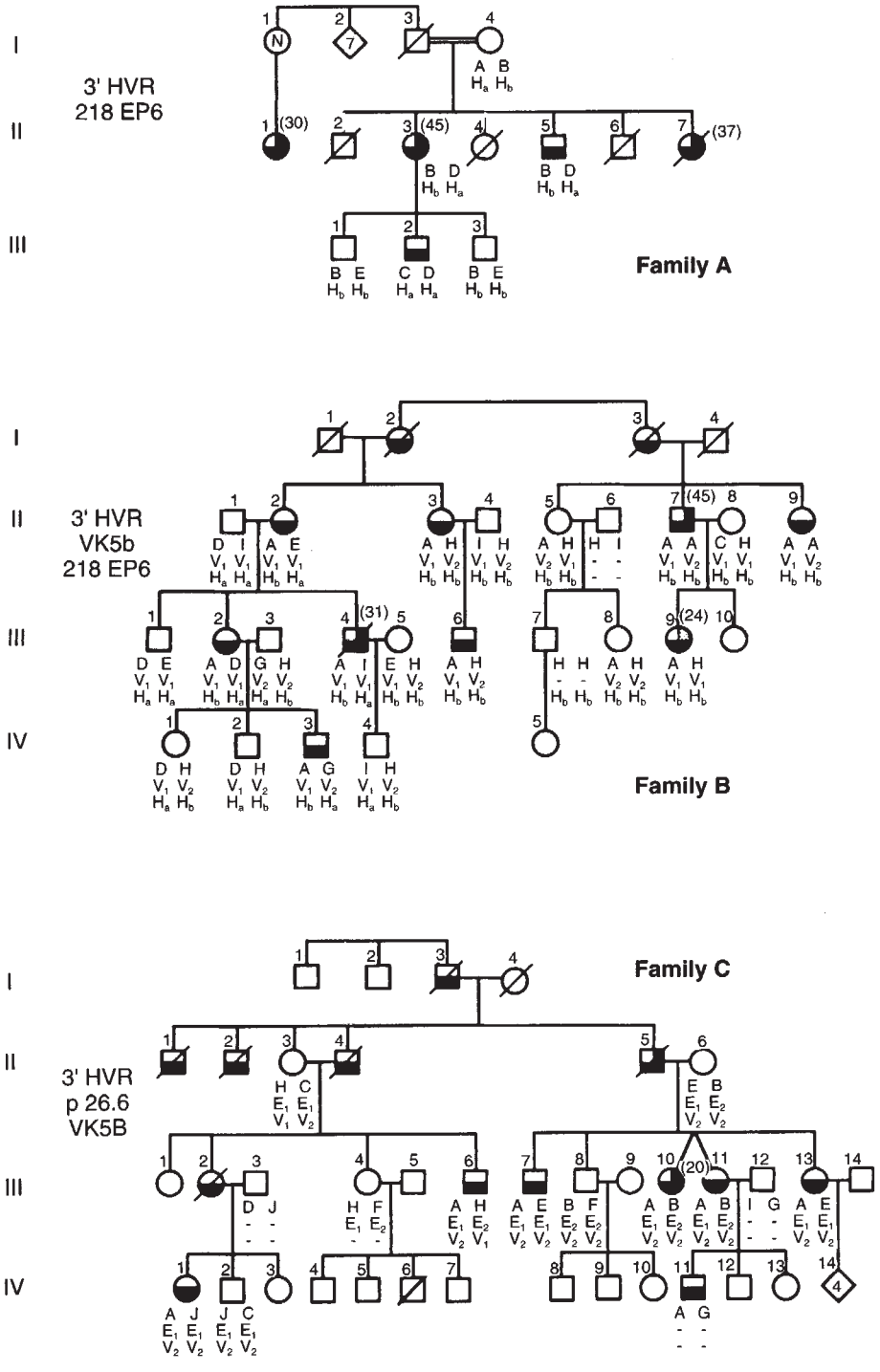

Fig. 2. *Pedigrees in three families with aneurysmal rupture in two or more relatives.* Symbols are: (◪◒) male and female with ADPKD; (◪●) ruptured intracranial aneurysm; (◒) unruptured intracranial aneurysm; (31) age at discovery of aneurysm; (N or ◇) not examined.

hemorrhage may have not been investigated as well. Despite typical presentation, patients with angiogram-negative subarachnoid hemorrhage were excluded. Furthermore, heterogeneity inherent to the multicenter design of the study probably affected the accuracy of collecting family histories and the approach to medical and surgical management of ICA among participating institutions. This must be kept in mind to interpret our results.

Despite these shortcomings, our study provides valuable information on the clinical profile of a large number of ADPKD patients with aneurysm rupture. We found that aneurysm rupture may be the initial manifestation of ADPKD. This event is not restricted to patients with advanced renal disease as 29% were normotensive and 50% had normal renal function at the time of the rupture. It may occur in youth: 10% of the patients were 20-years-old or less. To our knowledge, the youngest ADPKD patient reported with subarachnoid bleeding was a 6-year-old boy [15]. Female preponderance at a young age is characteristic of ruptured intracranial aneurysm in ADPKD and has not been observed in patients without ADPKD.

Aneurysm rupture entails a 46% risk of morbidity and mortality at three months in ADPKD patients. This is close to the corresponding figure in non-ADPKD patients, which ranges from 33 to 47% at six months in large surveys [16, 17]. At six months, a 55% mortality rate of subarachnoidal hemorrhage in ADPKD has been reported [13]. Indeed a less favorable outcome in ADPKD patients is to be expected because of the high prevalence of both hypertension and renal failure. Low blood pressure level at admission has been associated to be related to a favorable outcome in aneurysm rupture among non-ADPKD patients [17]. In our series, although chronic hypertension had been diagnosed in 71% of 38 patients whose blood pressure had been recorded within one year prior to rupture, we were not aware of blood pressure at admission. Poor outcome (death or severe neurologic impairment) was in the same range in previously normotensive and hypertensive patients (54 and 51%, respectively). From our series we thus cannot categorically assess the effect of blood pressure on outcome. Renal failure, present in 50% of our patients but in only 0.6% of the Cooperative Study [17], may conceivably worsen the prognosis initially by facilitating protracted bleeding or premature rebleeding because of the well-known platelet dysfunction related to uremia, or by increasing the complexity of medical management at a later stage. The case-fatality rates at three months were 15% and 6% among patients with renal failure or normal renal function, respectively. On the other hand, mean age at rupture in ADPKD patients was ten years below that reported in non-ADPKD patients [17] which may have, in turn, shifted toward a better outcome in our patients.

Once ruptured, whatever the size of the intracranial aneurysm, it must be selectively excluded from the cerebral circulation to prevent further bleeding, usually by clipping at the neck. In some centers, endovascular obliteration or parent vessel occlusion has been used in aneurysm with a large neck or in otherwise untreatable lesions, mainly of the posterior circulation [18]. Both procedures carry a significant risk. Our cumulative post-operative mortality rate of 9% is close to that reported in non-ADPKD patients [17]. Recent data suggest that mortality could be reduced by using drugs able to prevent vasospasm and limit cerebral ischemia, such as certain calcium antagonists [19].

A striking finding that emerges from this study is the risk of recurrent hemorrhage from another aneurysm on long-term follow-up. Such an event was observed in five cases. Of interest in three of them the aneurysm responsible for the second rupture was not detected at the time of the first one [11]. This phenomenon may have several explanations. The possibility that a second aneurysm was missed [20] on both pre- and postoperative angiogram seems unlikely. Progressive enlargement of a pre-existent microaneurysm, or rapid growth of a new aneurysm are more likely explanations. Whatever the mechanism, it is clear that intracranial aneurysm may develop over time in ADPKD. Taken together with the multiplicity of aneurysms (26% in this series, a figure close to the 18 to 19% reported elsewhere [17, 20]) these findings suggest that intracranial aneurysms reflect a diffuse and progressive disease of the cerebral arterial tree in ADPKD. On clinical practice, it implicates that ADPKD patients who have suffered ICA rupture should be regularly examined to detect the growth of new aneurysms.

The importance of heredity in the development of berry aneurysms has repeatedly been reported in non-ADPKD families with several relatives having ruptured aneurysms [21–23]. One recent study concluded that 7% of all ICA may be familial [24]. A dominant pattern of inheritance has been suggested [21, 23]. No chromosomal assignment has so far been reported. In ADPKD patients, we found a family history of aneurysm rupture in 10 out of 55 index cases (18%), a figure in keeping with the 22% familial prevalence reported by Schievink et al [13]. However, criteria for diagnosis of aneurysm rupture in relatives were not provided in the latter study. In the present series aneurysm rupture in one or more relatives was documented in six families by angiogram, and was considered as highly probable in four other families on the basis of subarachnoid hemorrhage occurring before the age of 40 years. This upper age limit was chosen to preclude the inclusion of relatives with stroke mimicking but unrelated to aneurysm rupture.

Familial aggregation of cerebral aneurysm is suggested by two of our families (Fig. 2, family A and B) as well as in two previously reported observations [25, 26] in whom more than two ADPKD-affected relatives also had intracranial aneurysm. It is unlikely that such clusters arose by chance alone. The young age of the affected patients provides further support to attributing the formation of aneurysms or subsequent growth to a genetic predisposition in ADPKD. Further evidence for familial clustering of cerebral aneurysm was recently given using magnetic resonance (MR) angiography in asymptomatic ADPKD patients which suggested a 4.4 relative risk if a positive family history of ICA is elicited [13]. Analysis of our pedigrees is consistent with a dominant pattern of inheritance.

Genetic analysis performed in two families strongly suggests that the disease is linked to the PKD1 locus. This association is not unexpected as the PKD1 gene accounts for 85% of ADPKD in Europe [27]. Whether specific mutations of the PKD1 gene are associated with cerebral aneurysm and may account for phenotypic heterogeneity between families warrants direct identification of the responsible gene(s). Interestingly, aneurysm rupture also affected only one single member of a large APDKD family unlinked to the PKD1 locus [2].

The biochemical abnormality leading to the formation of saccular ICA has never been studied in ADPKD. Collagen type III abnormalities have been demonstrated in half of patients with ICA in the absence of widespread connective tissue disorder [28]. Cerebral aneurysms may also be part of two dominantly inherited connective tissue disorders, the vascular form of Ehlers-Danlos syndrome (type IV) which results from a mutation in the gene for type III procollagen and Marfan's syndrome. These data suggest that collagen genes could also be candidate genes for ICA associated to ADPKD.

If genetic susceptibility to cerebral aneurysms exists in ADPKD, the reason for the low incidence of familial clusters of ICA rupture is not clear. It is tempting to attribute a significant role to environmental factors in the growth and subsequent rupture of ICA. Their influence could account for both the high prevalence of sporadic cases and non-concomitant development of cerebral aneurysm in identical twins in family C. As suggested by twins' history, uncontrolled hypertension could have promoted aneurysm enlargement in one of them. Apart

from hypertension, cigarette smoking [29] and alcohol consumption are also thought to be risk factors for subarachnoid hemorrhage in non-ADPKD patients.

Despite improvement in neuroanesthetic and surgical or endovascular procedures, a decline in mortality after aneurysmal rupture remains disputed [14], raising the question of investigation for occult aneurysm in ADPKD patients. From a practical point of view, no renal or extrarenal manifestation of ADPKD was found to be of value to predict the rupture of cerebral aneurysm; renal disease was unremarkable and liver cysts and mitral-valve abnormalities were not more frequent in our patients than in the general ADPKD population [30, 31]. This study was not designed to assess an association between severe polycystic liver disease and cerebral aneurysm suggested in a single study [7]. The question of routine screening for ICA with cerebral angiography was assessed by Levey, Pauker and Kassirer. Using decision analysis they concluded that such screening was not warranted in all ADPKD patient [32]. Furthermore, the use of this technique might be associated with a higher complication rate in ADPKD [12]. Noninvasive tests such as CT-scan and MR imaging are of limited values because of their low specificity to diagnose small ICA [7, 12]. MR angiography, which can define the circle of Willis sufficiently to detect cerebral aneurysms as small as 1.5 mm, has been performed in a series of 85 asymptomatic ADPKD patients and detected a definite aneurysm in nine (11%) [7]. The size of the aneurysms was less than 6.5 mm in diameter. Most neurosurgeons would be reluctant to perform prophylactic cure of aneurysms measuring less than 10 mm in diameter, because the annual risk of rupture is known to be low. It thus appears that widespread screening examination in unselected ADPKD patients remains unrewarding. It seems reasonable to restrict noninvasive screening for occult aneurysms to patients at high risk of development of ICA. There is no doubt that patients surviving a first rupture must be regularly restudied. Due to the possibility of familial clustering, prophylactic investigation should be performed in asymptomatic patients having two relatives or more who have experienced aneurysm rupture. In view of our data, we suggest that such screening start as early as 18 years of age. These recommendations might apply as well to those with only one affected relative. A prospective study is anyway required to prove the usefulness of familial screening and the periodicity of repeated examination. Screening in asymptomatic patients has also been advocated in individual setting, such as major vascular surgery [33].

Obviously, all patients with the classic presentation of subarachnoid hemorrhage must be rapidly investigated. The diagnostic importance of a warning headache in non-ADPKD patients has been emphasized [34]. A sentinel aneurysmal leak should indeed be suspected in a patient with severe unusual pain in the head or face. It could precede by weeks or months as many as half of the cases of aneurysm rupture. Every ADPKD patient should be aware of the meaning of such symptomatology.

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